HALL
Dick Schmitt

JAN 14 Minutes

THE DOW CHEMICAL COMPANY

POST OFFICE BOX 1706
MIDLAND, MICHIGAN 48640

February 23, 1981

Dr. Ronald D. Wilson
Rhone-Poulenc Inc.
P.O. Box 124
Monmouth Junction, NJ 08852

Dr. Don Munger
Diamond Shamrock Corporation
1100 Superior Avenue
Cleveland, OH 44114

Dr. Don Yoder
BASF Wyandotte Corporation
100 Cherry Hill Road
Parsippany, NJ 07054

[redacted]
Environmental Protection Agency
Special Pesticide Review Division
TS 791
401 M. Street SW
Washington, D.C. 20460

Mr. John Wise
Farmland Industries, Inc.
P.O. Box 7035
Kansas City, MO 64116

Dr. L. J. Reid
VERTAC Chemical Corporation
5100 Poplar Avenue
Suite 2414
Memphis, TN 38137

Mr. J. S. Skaptason
PBI Gordon Corporation
P.O. Box 2276
300 S. Third St.
Kansas City, KS 66110

Dr. Ray D. Cardona
Uniroyal Chemical
Amity Road
Bethany, CT 06525

Mr. Tim Pomeroy
Transbas, Inc.
P.O. Box 957
Billings, MT 59103

Mr. Wayne Ormrod
Associate Director Pesticide
Section
Food Production & Inspection Branch
Agriculture Canada, Ottawa, KLA 0C6
CANADA

Attached are the minutes of the January 14, 1981 meeting for your consideration.

Sincerely,

John W. Weseloh

John W. Weseloh
Chairman, 2,4-D Technical Committee

cbg

Enclosure

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February 10, 1981

RECEIVED
FEB 16 1981
REGISTRATION

Mr. John W. Weseloh
Manager, Product Registrations
The Dow Chemical Company
Midland, Michigan 48640

Dear John:

Enclosed is a copy of the minutes of the January 14, 1981 meeting of the Technical Committee, together with exhibits.

Pursuant to the minutes of the January 23, 1981 meeting of the Technical Committee and L. B. Westover's letter of February 2, 1981, once we receive samples, we will assign each set of five sample bottles a code and forward the set to the four laboratories identified in the February 2, 1981 minutes. Unless I receive instructions from you to the contrary, we will forward to the laboratories each set as we receive them, after they have been assigned a code. We will not wait until we have received all nine sets before forwarding them to the four laboratories.

For your information, as of today, the following companies have executed and returned to us the Memorandum of Understanding:

1. Farmland Industries, Inc.
2. Rhone-Poulenc, Inc.
3. Dow Chemical Company
4. BASF Wyandotte Corp.
5. PBI-Gordon Corp.

LAW OFFICES
McKENNA, CONNER & CUNEO

Should you have any questions or comments, please feel free to contact me.

With best regards.

Sincerely,

John D. Conner, Jr.

Enclosures
JDC,jr:das

cc: John Davies

INDUSTRY TASK FORCE ON 2,4-D RESEARCH DATA

Meeting of the Technical Committee
MC&C Conference Room

Washington, D.C. -- January 14, 1981

M I N U T E S

TIME/PLACE

The meeting of the Technical Committee of the Industry Task Force on 2,4-D Research Data was held at 9 a.m. on January 14, 1981 at the Conference Room of McKenna, Conner & Cuneo, Washington, D.C.

ATTENDANCE

John W. Weseloh (Chairman)	- Dow Chemical Company
Ray D. Cardona	- Uniroyal Chemical
Dan Miller	- Farmland Industries
Werner H. Braun	- Dow Chemical Company
Dick Kociba	- Dow Chemical Company
John M. Wise	- Farmland Industries
G. Donald Munger	- Diamond Shamrock
J. S. Skaptason	- PBI Gordon Corp.
Patricia Cohn	- EPA
Henry Spencer	- EPA
Wayne Ormrod	- Agriculture Canada
Ronald D. Wilson	- Rhone-Poulenc, Inc.
Jim L. Reid	- Vertac
John Conner, Jr.	- McKenna, Conner & Cuneo

CALL TO ORDER

The meeting of the Technical Committee was called to order at 9 a.m. by John Weseloh, Chairman of Technical Committee. John D. Conner, Jr. was present as Secretary.

WELCOME TO WAYNE ORMROD

John Weseloh welcomed Wayne Ormrod, Associate Director Pesticide Section, Agriculture Canada, to the meeting.

MINUTES OF DECEMBER 17, 1980

The minutes of December 17, 1980 were approved without amendment.

90-DAY FEEDING STUDY

Dick Kociba of Dow summarized the results of Dow's two subchronic studies of 2,4-D dichlorophenoxyacetic acid in rats. Transparency handouts summarizing Dr. Kociba's presentation are attached as Exhibit 1.

METABOLISM STUDY

Werner H. Braun of Dow discussed the results of two oral and dermal 2,4-D metabolism studies in the rat and identified the need for additional metabolism studies.

RECOMMENDED DOSE FOR 2-YEAR STUDY

Dr. Kociba recommended that the laboratory that performs the two-year studies also perform a ninety-day study to determine the proper doses for the long-term testing.

SPECIES AND TEST SUBSTANCES RECOMMENDATIONS .

In response to Dr. Braun's observation that different esters should be used in the teratology testing than the esters recommended by EPA and that the dog is not a good species for neurotoxicity testing, Pat Cohn requested that the Task Force provide EPA with a proposal describing how the Task Force wants to conduct certain testing. Dr. Braun will submit such a proposal as a counter proposal to EPA's requirements.

ACUTE TESTING

Pat Cohn distributed and reviewed an undated letter from EPA to registrants on the subject of acute testing. See, Exhibit 2.

As a Task Force, a response will be sent to EPA pursuant to option B in the EPA letter.

RON WILSON

Ron Wilson has received laboratory recommendations from two companies. Pat Cohn will notify Ron Wilson if there are problems with any of the labs.

DIOXIN ANALYSIS

J. Weseloh distributed Exhibit 3, "Protocol for Development of a Method to Analysis 2,4-D Acid for the Presence of Dioxins" and Exhibit 4, "Determination of Chlorinated Dibenzo-p-dioxins in Purified Pentachlorophenol by Liquid Chromatography."

Mr. Ormrod of Agriculture Canada questioned the acceptability of a dioxin analytical method sensitive to .1 ppm. It was pointed out that analytical equipment at industry level was not sensitive at a level below .1 ppm.

INFORMATION TO BE MADE AVAILABLE BY AG CANADA

Wayne Ormrod stated that the following Canadian materials would be made available to members of the Task Force: (1) Canadian health and welfare review; (2) Canadian dioxin study; (3) use patterns; (4) data requirements of Canada; (5) policy position of Canada on confidential data; (6) FOIA proposal in Canada.

ANALYSIS OF 2,4-D PRODUCTS TO THE PRESENCE OF DIOXINS

John Weseloh again announced the scheduled meeting for January 23, 1981 which was called for the purpose of discussing the analysis of 2,4-D products for the presence of dioxins. John Weseloh emphasized the necessity of developing a validated method of analysis for dioxins, in order to establish operational levels and limits for quality control. John Weseloh emphasized that .1 ppm was chosen as a specification limit because of the tight schedule for testing.

NEXT MEETING

The next meeting will be held in March, 1981.

ADJOURNMENT

The meeting adjourned at 2:15 p.m.

John D. Conner, Jr.

Attachments

SUBCHRONIC DIETARY STUDIES OF TECHNICAL GRADE OR PURIFIED 2,4-DICHLOROPHENOXYACETIC ACID

SPECIES - FISCHER 344 RATS (MALE AND FEMALE)

ROUTE OF EXPOSURE - CONTINUOUS INGESTION OF DIETS CONTAINING TECHNICAL GRADE OR PURIFIED 2,4-D

DURATION - 13 WEEKS

DOSE LEVELS - 0, 15, 60, 100, OR 150 MG 2,4-D/KG BODY WEIGHT/DAY

GROUP SIZES - 15/SEX - EACH TREATMENT GROUP
15/SEX - CONTROL GROUP

TWO SUBCHRONIC STUDIES OF 2,4-DICHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF TREATMENT-RELATED CHANGES

PARAMETER	TECHNICAL GRADE 2,4-D DOSE MG/KG/DAY				PURIFIED 2,4-D (PRELIMINARY ASSESSMENT) DOSE MG/KG/DAY			
	15	60	100	150	15	60	100	150
SIGNS OF TOXICITY	--	--	--	--	--	--	--	--
BODY WEIGHT (MEAN)	--	--	↓F	↓M,F	--	↓F	↓M,F	↓M,F
BODY WEIGHT GAIN	--	--	↓F	↓M,F		NOT COMPLETED		
FOOD CONSUMPTION	--	--	↓F	↓F	--	--	--	↓M,F
FOOD CONVERSION $\left(\frac{\text{WEIGHT GAIN}}{\text{FOOD CONSUMED}}\right)$	--	--	--	↓M,F		NOT COMPLETED		

-- NO EFFECTS DIRECTLY RELATED TO TREATMENT.

TWO SUBCHRONIC STUDIES OF 2,4-DICHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF TREATMENT-RELATED CHANGES

PARAMETER	TECHNICAL GRADE 2,4-D DOSE MG/KG/DAY				PURIFIED 2,4-D (PRELIMINARY ASSESSMENT) DOSE MG/KG/DAY			
	15	60	100	150	15	60	100	150
CLINICAL CHEMISTRY								
BUN	--	--	--	--	--	--	--	--
SGPT	--	--	↑ F	↑ M,F	--	±↑F	↑ F	↑M, ±↑F
AP	--	--	--	↓?F	↓?F	--	--	↓?F
GLUCOSE	--	--	--	--	--	--	↓ M,F	↓M,F
TOTAL PROTEIN*	--	--	--	--	--	--	--	--
ALBUMIN*	--	--	--	--	--	--	--	--
GLOBULIN	--	--	--	--	--	--	--	--
TETRAIODOTHYROXINE (T4)	↑?F --	↑?F --	↓F ↑?M	↓F --	-- ↑?M	↓F ↑?M	↓F ↑?M	↓F --
HEMATOLOGY (PCV, RBC, HGB, WBC, DIFF.)	N.D.	N.D.	N.D.	--	--	--	--	--
URINALYSIS (SPECIFIC GRAVITY, PH, GLUCOSE, KETONES, BILIRUBIN, OCCULT BLOOD, UROBILINOGEN)	N.D.	N.D.	N.D.	--	N.D.	N.D	N.D.	--

-- NO EFFECTS DIRECTLY RELATED TO TREATMENT.
N.D. = NOT EVALUATED.
*SOME GROUPS AT HIGHER DOSE LEVELS HAD STATISTICAL INCREASES ABOVE CONTROL.

TWO SUBCHRONIC STUDIES OF 2,4-DICHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF TREATMENT-RELATED CHANGES

Parameter	Technical Grade 2,4-D Dose mg/kg/day				Purified 2,4-D (Preliminary Assessment) Dose mg/kg/day			
	15	60	100	150	15	60	100	150
Organ Weights								
Brain - absolute	--	--	--	--	--	--	--	--
- relative	--	--	--	--	--	--	--	--
Heart - absolute	--	--	--	--	--	--	--	--
- relative	--	--	--	--	--	--	--	--
Liver - absolute	--	--	--	--	--	--	--	--
- relative	--	--	--	↑ F	--	↑ F	↑ F	↑ F
Kidneys - absolute	--	↑ M	↑ M	↑ M	--	↑ M	↑ M,F	↑ F
- relative	↑ M	↑ M	↑ M	↑ M,F	↑ M	↑ M,F	↑ M,F	↑ M,F
Thymus - absolute	--	--	--	↓ F	--	--	--	↓ F
- relative	--	--	--	↓ F	--	--	--	--
Testes - absolute	--	--	--	--	--	--	--	--
relative	--	--	--	--	--	--	--	--

-- No effects directly related to treatment.

TWO SUBCHRONIC STUDIES OF 2,4-DICHLOROPHENOXYACETIC ACID IN RATS
SUMMARY OF TREATMENT-RELATED CHANGES

PARAMETER	TECHNICAL GRADE 2,4-D DOSE MG/KG/DAY				PURIFIED 2,4-D (PRELIMINARY ASSESSMENT) DOSE MG/KG/DAY			
	15	60	100	150	15	60	100	150
GROSS PATHOLOGY								
KIDNEYS - SLIGHT SWELLING	--	--	±M	M,F	--	F	F	M,F
DECREASED ADIPOSE TISSUE	--	--	--	F	--	--	--	M
DECREASED BODY SIZE	--	--	--	F	--	--	-	M
GASTRIC EROSION/HEMORRHAGE	--	--	--	F	--	--	--	--
HISTOPATHOLOGY								
LIVER - HEPATOCELLULAR CHANGES - DIFFUSE, SLIGHT	--	--	--	M,F	--	--	--	--
- DIFFUSE, VERY SLIGHT	--	--	M,F	--	--	--	--	--
- DIFFUSE, EQUIVOCAL TO SLIGHT	--	--	--	--	--	--	M,F	M,F
KIDNEYS - SLIGHT CYTOPLASMIC CHANGES IN CONVOLUTED TUBULES								
- INCREASED HOMOGENIETY								
- DIFFUSE	--	--	--	M	--	--	M	M
- MULTIFOCAL	--	--	M	--	--	M	M	--
- FOCAL	--	M	--	--	--	M	M	--
- INCREASED EPITHELIAL VACUOLATIZATION								
- MULTIFOCAL	--	--	--	F	--	--	F	F
- FOCAL	--	F	F	--	F	F	F	F

-- NO EFFECTS DIRECTLY RELATED TO TREATMENT.

TECHNICAL 2,4-D - SUMMARY OF TREATMENT-RELATED CHANGES IN RATS

TREATMENT-RELATED CHANGES IN:	DOSE (MG/KG/DAY) 15	60	100	150
BODY WEIGHT	--	--	↓ F	↓M,F
FOOD CONSUMPTION	--	--	↓ F	↓ F
FOOD CONVERSION	--	--	--	↓M,F
CLINICAL CHEMISTRY				
SGPT	--	--	↑ F	↑M,F
AP	--	--	--	↓ F
TOTAL PROTEIN	--	--	--	T↑F
ALBUMIN	--	--	T↑F	T↑F
T_4	↑?F	↑ ?F	↓ F	↓F
	--	--	↑?M	--
ORGAN WEIGHTS				
LIVER - ABSOLUTE	--	--	--	--
- RELATIVE	--	--	--	↑ F
KIDNEYS - ABSOLUTE	--	↑ M	↑ M	↑ M
- RELATIVE	↑ M	↑ M	↑ M	↑M,F
THYMUS - ABSOLUTE	--	--	--	↓ F
- RELATIVE	--	--	--	↓ F
GROSS PATHOLOGY				
KIDNEYS - SLIGHT SWELLING	--	--	--	M,F
DECREASED ADIPOSE TISSUE	--	--	--	F
DECREASED BODY SIZE	--	--	--	F
STOMACH - EROSION/HEMORRHAGE	--	--	--	F
HISTOPATHOLOGY				
LIVER - HEPATOCELLULAR CHANGES				
- DIFFUSE, SLIGHT	--	--	--	M,F
- DIFFUSE, VERY SLIGHT	--	--	M,F	--
KIDNEYS - SLIGHT CYTOPLASMIC CHANGES IN CONVOLUTED TUBULES				
- DIFFUSE	--	--	--	M,F
- MULTIFOCAL	--	--	M	--
- FOCAL	--	M,F	F	--

PURIFIED 2,4-D - SUMMARY OF TREATMENT-RELATED CHANGES IN RATS

(PRELIMINARY ASSESSMENT)

TREATMENT-RELATED CHANGES IN:	DOSE (MG/KG/DAY) 15	50	100	150
BODY WEIGHT (MEAN)	--	↓ F	↓ M,F	↓ M,F
FOOD CONSUMPTION	--	--	--	↓ M,F
CLINICAL CHEMISTRY				
SGPT	--	±↑F	↑ F	↑M,±↑F
AP	--	--	--	↓?F
GLUCOSE	--	--	↓M,F	↓M,F
ALBUMIN	--	--	--	--
T_4	—	↓ F	↓ F	↓ F
	↑?M	↑?M	↑?M	--
ORGAN WEIGHTS				
LIVER - ABSOLUTE	--	--	--	--
- RELATIVE	--	↑ F	↑ F	↑ F
KIDNEYS - ABSOLUTE	--	↑ M	↑ M,F	↑ F
- RELATIVE	↑ M	↑ M,F	↑M,F	↑M,F
THYMUS - ABSOLUTE	--	--	--	↓ F
GROSS PATHOLOGY				
KIDNEYS - SLIGHT SWELLING	--	F	F	M,F
DECREASED ADIPOSE TISSUE	--	--	--	M
DECREASED BODY SIZE	--	--	--	M
HISTOPATHOLOGY				
LIVER - HEPATOCELLULAR CHANGES				
- DIFFUSE, EQUIVOCAL	--	--	M,F	M,F
- DIFFUSE, SLIGHT	--	--	F	F
KIDNEYS - SLIGHT CYTOPLASMIC CHANGES IN CONVOLUTED TUBULES				
- DIFFUSE	--	--	M	M
- MULTIFOCAL	--	M	M,F	F
- FOCAL	F	M,F	M,F	F

EXHIBIT 2

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

ORDER AND NOTICE

Dear Registrant:

In the August 29, 1980 ORDER AND NOTICE issued under Section (3)(c)(2)(B) of the Federal Insecticide, Fungicide and Rodenticide Act, 7 U.S.C. 136a (c)(2)(B), EPA informed registrants of 2,4-D products of a variety of data-submission requirements. This letter modifies some aspects of our original request for data and clarifies other requirements that may not have been fully understood by registrants. Except for changes made in this letter, the original ORDER AND NOTICE remains in effect.

First, the Agency is deferring the requirement for the studies on acute oral toxicity and acute dermal toxicity of end-use products containing 2,4-D. The Agency will group the 2,4-D end-use products and require testing on a representative sample for each group. This action will achieve a better balance between the Agency's need for more data on acute toxicity and the Agency's desire to avoid the unnecessary duplication of data. It will also relieve small manufacturers of the burden of producing data for each of the numerous end-use products.

In this way, the information needed can be generated by fewer studies. The lower cost of this reduced number of studies can be shared among the registrants. EPA will inform registrants of the revised requirements and the timetable for submission of data at a later date.

Registrants of manufacturing-use products are still required to submit acute oral and dermal toxicity studies for those products. The Agency has grouped these products (see Appendix I), and registrants may cooperate to produce one set of tests for each group. The terms of the August 29 ORDER AND NOTICE continue to apply to these acute studies. The schedule for submission of these studies is May 1, 1981. Registrants may request a time extension, if necessary, with an adequate rationale. The registrants of manufacturing-use products should refer to the August ORDER AND NOTICE for detailed guidance. Page 3 of the earlier ORDER AND NOTICE requires registrants to respond in one of six ways for each product.

These six options, with comments explaining why some of the options are not appropriate responses to this request for acute toxicity data, are:

(A) You must notify EPA that you are willing to produce and submit the data yourself;

(B) You must notify EPA that you have entered into an agreement, with one or more of the other registrants who are subject to this notice's requirements, to jointly produce and submit the data, or to share in the cost of this work;

(C) You must provide to EPA the "Statement of Willingness to Enter Into an Agreement with Other Registrants for Development of Data", in accordance with Section V and Appendix C of the August 29th ORDER AND NOTICE, which will allow EPA to exempt you, under certain circumstances, from the consequences of not submitting some or all of these data;

Options (B) and (C) apply to joint studies of a single test substance that serve to meet data submission requirements for two or more products. These options are appropriate for products which have been grouped together. Registrants may jointly produce the data for each group, or a registrant may choose to produce acute oral and dermal toxicity studies for his own product;

(D) This option applies only to end-use products;

(E) This option provides for waiver requests. The studies being requested on acute oral and dermal toxicity provide the minimum amount of information on such toxicity that is acceptable to the Agency. By thus reducing the scope of the request for such data, EPA thinks that it has eliminated the circumstances under which waiver requests can be justified. Accordingly, the Agency does not contemplate granting waivers of these minimum requirements for data production.

(F) You must file with EPA a request that the registration(s) for your products containing any or all forms of 2,4-D be voluntarily cancelled.

If a registrant has an existing study which may fill one of the requirements in this Notice, that study may be submitted to the Agency. We will promptly review the study to determine if it is scientifically valid and satisfies the requirement.

Registrants of manufacturing-use products have 30 days from receipt of this letter to respond to the requirement for acute oral and acute dermal toxicity tests on each manufacturing-use product. If your company has registered manufacturing-use products, a list of manufacturing-use products and registrants is attached to this notice. You may use this list to identify products for which joint data production is appropriate. (Appendix II). If affected registrants do not respond within 30 days, the Agency may suspend their registrations as stated in the earlier ORDER AND NOTICE.

Registrants are also reminded that dermal absorption studies on some liquid and emulsifiable concentrate end-use products will still be required, as mentioned in the August 29th ORDER AND NOTICE. EPA is developing a protocol for these studies, and consolidating these data requirements so that each end-use product need not be tested. As in the case of the acute oral and dermal toxicity data requirements, this action will substantially reduce the number of studies to be done, avoiding needless duplication of data and unnecessary hardship on small manufacturers. Registrants will be notified at a later date of the protocol to be followed, the revised data requirements, and the scheduled date for submission of the studies.

If you have any questions concerning this letter, or the orginial ORDER AND NOTICE, you may contact Patricia Cohn at (703) 557-7973 for further information.

Sincerely yours,

Edwin L. Johnson
Deputy Assistant Administrator
for Pesticide Programs

APPENDIX I

Grouping of 2,4-D Manufacturing-Use Products for Acute Oral and Dermal Testing

The Agency will accept one set of acute oral and acute dermal toxicity tests for each group of products identified below. The basis for developing these groups is that the Agency anticipates one set of acute oral and dermal LD_{50} values will adequately represent all products in the group. The Agency may require additional actue toxicity tests within a group if a review of the single set of tests indicates that they may not be representative of all products in the group.

The products that the Agency will accept as the test substance for each group are indicated with an asterisk.* Any registrant may choose to test his own product rather than to participate in testing the representative product for the group.

Note: Products containing silvex are suspended, therefore no testing is required on these products at this time.

Acute oral and dermal toxicity studies are not being required on formulation interimediates in granular form.

2,4-Dichlorophenoxyacetic acid technical grade

Product numbers

148 - 1226*

264 - 247*

359 - 579*

464 - 453*
464 - 454*

524 - 3* - this registration is being transferred to registrant number 34704

677 - 266*

2217 - 455*

6305 - 11*

7501 - 23* - this registration is being transferred to registrant number 400

7969 - 22*

39335 - 3

39335 - 30

39511 - 60

In order to determine whether the following two technical grade 2,4-D acids may be grouped with the above products, the Agency must receive an accurate, current confidential statement of formula for these products within 15 days from receipt of this letter. The Agency will promptly review the Confidential Statements of formula and notify registrants whether they may participate in the above group or must produce separate acute toxicity tests. If the Agency does not receive the Confidential Statements of formula the registrants must produce separate acute oral and dermal toxicity tests for each of these two products.

2217-632

7969 -29

Sodium 2,4 Dichlorophenoxyacetate technical grade and formulation intermediate

228 - 123*

39335 - 26

Isooctyl (2 ethyl hexyl) 2,4 dichlorophenoxyacetate technical grade

148 - 926*

228 - 126*

464 - 458*

524 - 94* - this product is being transferred to registrant number 34704

677 - 251*

677 - 255*

39511 - 62*

40831 - 119*

Isooctyl (2 octyl) 2,4-dichlorophenoxyacetate technical grade

359 - 577*

Butyl 2,4-dichlorophenoxyacetate technical grade

228 - 128*

359 - 584*

464 - 456*

524 - 62* this registration is being transferred to registrant number 34704

677 - 252*

39511 - 61*

Isobutyl 2,4-dichlorophenoxyacetate technical grade

148 - 927*

Butoxyethyl 2,4-dichlorophenoxyacetate technical grade

228 - 136*

464 - 518

39511 - 63*

Isopropyl 2, 4-dichlorophenoxyacetate

677 - 249*

5481 - 144*

Formulation Intermediates - Dimethylamine

464 - 457 - this product must be tested

2217 - 488*
- 493
- 531
- 571
- 602
- 623
- 625

39335 - 27

2217 618 this product must be tested

Formulation Intermediates - Diethonolamine

2217 - 524 this product must be tested

2217 - 491 this product must be tested

Formulation Intermediate - Butoxyethyl 2,4-D

228 - 141 this product must be tested

EXHIBIT 3

PROTOCOL FOR DEVELOPMENT OF A METHOD TO ANALYZE 2,4-D ACID FOR THE PRESENCE OF DIOXINS

Compounds for which the method will be validated:

2,7-Di CDD*; 1,3,8-tri CDD*; 1,3,6,8-tetra CDD*; 2,3,7,8-tetra CDD

*Investigation may show that the method should also analyze for the Smiles rearrangement products of these compounds (the Smiles rearrangement products are 2,8-DCDD; 1,3,7-tri CDD; 1,3,7,9-tetra CDD).

Specification limit to be supported by method: 1 ppm

Method should be sensitive to 0.1 or 0.2 ppm to support this specification limit.

Type of method to be developed:

A high performance liquid chromatography (HPLC) method with ultraviolet detection will be developed if possible. This type of method is attractive because of relatively low equipment cost and suitability for use in a plant laboratory.

Standards:

Preparation and characterization of standards will need to be carried out at the same time as method development.

METHOD DEVELOPMENT

1. Confirm that development of an HPLC method is feasible.

   Analyze 2,4-D acid samples from the various producers by modifications of the method in Anal. Chem. 50, 800 (1978). The 2,4-D acid will be dissolved and extracted and the extract analyzed by HPLC.

   Dioxin reference compounds presently available will be used until analytical standards are prepared and validated.

   As part of the method development, if peaks of apparent concentration >0.1 or 0.2 ppm are present at the retention times of the dioxins being sought, the identity of the peaks will be checked by gas chromatography - low resolution mass spectrometry (GC-MS).

1a. If step 1 is not successful, additional cleanup of the extract with final HPLC examination will be tried.

2. If steps 1 or 1a are successful, the HPLC procedure will be studied to shorten it and optimize it. Initial experiments have shown that the probability of success is high.

   Parameters to be studied include:

   direct injection of extract without cleanup

   effect of extraction solvents

   effect of detector wavelength on sensitivity and interferences

   suitability of single wavelength detectors

   applicability of an integrator to the method

   modifications of the liquid chromatography mobile phase

   effect of temperature and temperature variations

3. Validation of method for the analysis of 2,4-D acid

   prepare 10 synthetic samples with known dioxin concentrations of 0.2 to 1.5 ppm

   analyze the synthetic samples by the proposed method

   calculate precision and accuracy for each dioxin being determined

   usual practices for generating validation data will be followed, i.e., analyses on different days and by different analysts

4. Collaborative testing

   An independent laboratory will test the suitability of the method

EXHIBIT 4

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Determination of Chlorinated Dibenzo-*p*-dioxins in Purified Pentachlorophenol by Liquid Chromatography

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A rapid liquid chromatographic method for the determination of hexa-, hepta-, and octachlorodibenzo-*p*-dioxins in pentachlorophenol is described. The nonphenolic impurities are quantitatively isolated from the sample matrix by an extraction–column chromatography procedure that permits the chlorinated dibenzo-*p*-dioxins to be determined by reverse-phase partition liquid chromatography. Sample concentrates are analyzed in a 12-min separation with detection limits of 100 parts per billion. The entire analysis may be completed in 60 min.

Numerous methods have been published for the determination of chlorinated dibenzo-*p*-dioxins (CDDs) in pentachlorophenol which is now widely used as a wood preservative and fungicide. Recent techniques used for this analysis have included gas chromatography with mass spectrometry, flame ionization or electron capture detection, and liquid chromatography with ultraviolet detection (*1–6*). The methods employing gas chromatography–mass spectrometry offer the greatest specificity and sensitivity. However, liquid chromatography remains an attractive alternative for analyzing samples on a routine basis because of the relatively low cost of the equipment required and the rapid separations possible.

The liquid chromatography method described previously (*5*) had two major limitations in that the separation was relatively slow requiring 40 min and the sensitivity for hexa-CDD was limited to approximately 0.5 ppm in typical samples. The objectives of the present work were to improve both the sensitivity and specificity of the method for hexa-CDD and reduce the liquid chromatography separation time.

EXPERIMENTAL

Reagents. Carbon tetrachloride, chloroform, methylene chloride, hexane, *o*-xylene, and methanol of distilled-in-glass quality were obtained from Burdick and Jackson Laboratories, Inc., Muskegon, Mich. Aqueous sodium hydroxide solutions were prepared by appropriate dilution of reagent grade 50% sodium hydroxide by weight obtained from J. T. Baker Chemical Co., Phillipsburg, N.J. Silicic acid as 100/200-mesh Bio-Sil A and basic alumina as 100/200-mesh Bio-Rad Basic Alumina AG-10 were obtained from Bio-Rad Laboratories, Richmond, Calif.

The Bio-Sil A adsorbent was dried in a temperature controlled tube furnace under continuous nitrogen purge (approximately 100 cm^3/min) at 180 °C for a period of 1.5 h. The basic alumina adsorbent was also dried in this apparatus at 280 °C for 1.5 h. Dried adsorbents were stored in capped glass bottles in a glass desiccator over phosphorus pentoxide to maintain their activity until used.

Chlorinated Dibenzo-*p*-dioxin Standards. The hexachlorodibenzo-*p*-dioxin (hexa-CDD), heptachlorodibenzo-*p*-dioxin (hepta-CDD), and octachlorodibenzo-*p*-dioxin (octa-CDD) used as standards were synthesized at the Dow Chemical Company. These materials were subjected to rigorous analysis by mass spectrometry, infrared spectrophotometry, nuclear magnetic resonance spectrometry, gas chromatography, and combined gas chromatography–mass spectrometry (GC-MS) to confirm their identity and purity. The hexa-CDD and octa-CDD were those compounds reported by Aniline (*7*). The purity of the hexa-CDD (a mixture of two isomers) was greater than 99%. The octa-CDD had a purity of 99.9% and also was examined by single crystal x-ray spectrometry for unequivocal proof of structure (*8*). The hepta-CDD, single isomer 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin, was prepared via the specific isomer synthesis reported by Grey (*9*). Its purity was greater than 98.5%.

Standard solutions of each CDD were prepared by weight in *o*-xylene at approximately the 200-ppm level. For liquid chromatographic analyses, appropriate aliquots were diluted with chloroform to yield a final mixture containing 0.2 to 1.5 μg/mL hexa-CDD, 5 to 15 μg/mL hepta-CDD, and 5 to 25 μg/mL octa-CDD. The same procedure using *o*-xylene as the diluent was used to produce standards of appropriate concentration for electron capture gas chromatography (GC-EC) and GC-MS analyses. *Caution. Extreme care must be taken to avoid skin* contact with either the standards or standard solutions. Gloves must be worn at all times when handling these compounds or concentrated extracts of materials believed to contain these species.

Apparatus. *Liquid Chromatograph.* The liquid chromatograph (LC) used was a modular system consisting of a Waters Associates model M-6000A pump, a Rheodyne model 7120 sample injection valve, and a Perkin-Elmer model LC-55 or LC-65T variable wavelength ultraviolet detector. The microparticulate, reverse-phase column used was a 4.6 × 250-mm ODS/Zorbax (6μ, *DuPont Instruments). It was purchased prepacked from the* supplier and used as received. The LC operational parameters were: mobile phase, methanol; mobile phase flow rate, 2.0 mL/min; column temperature, ambient; detector wavelength, 245 nm; detector sensitivity, 0.02 AUFS, injection, 6 μL.

Gas Chromatograph (GC-EC). A Varian Series 3700 Gas Chromatograph equipped with an Aerograph ^{63}Ni Pulsed Electron Capture Detector was used. A 2-mm i.d. × 350-cm glass column was cleaned and deactivated by dimethyldichlorosilane treatment, then packed using gentle vacuum and a vibrator. The column packing consisted of a binary stationary phase mixture: 0.60%

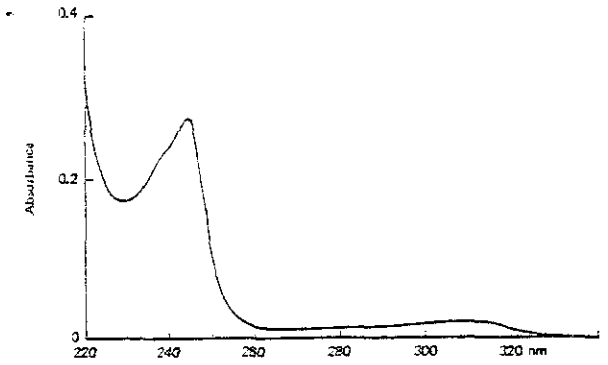

Figure 1. Ultraviolet spectrum of hexachloridibenzo-*p*-dioxin. Solvent, methanol; reference, methanol; cell path, 1.00 cm

OV-17 silicone and 0.40% Poly S-179, coated on specially deactivated 80/100 mesh Chromosorb W-AW using a slurry procedure with chloroform as the solvent. The column was conditioned for approximately 24 h at 320 °C with 35 cm^3/min nitrogen carrier gas flow prior to use. All injections were made on-column under the following conditions: column temperature, programmed from 170 to 290 °C at 5 °C/min (hold at maximum); carrier flow rate, 25 cm^3/min; injection port temperature, 250 °C; detector temperature, 320 °C; and electrometer sensitivity, 64 to 128 × 10.

Gas Chromatograph–Mass Spectrometer (GC-MS). A Finnigan model 3000 quadrupole mass spectrometer equipped with a venting system, glass-jet separator interface, and a 4-ion programmable multiple-ion monitor was used. The gas chromatographic column, packing, and operational parameters were the same as described for GC-EC, except for carrier gas and flow rate which were helium at 30 cm^3/min. Polychlorinated benzenes, polychlorinated biphenyls, polychlorinated diphenyl ethers, polychlorinated dibenzofurans, and polychlorinated dibenzo-*p*-dioxins were identified by mass fragmentography at selected *m/e* values in accordance with data published by Buser (*2*).

Liquid Chromatography Adsorbent Columns. The silicic acid and basic alumina cleanup columns were prepared in 5-mm i.d. × 150-mm glass disposable capillary pipets available from VWR Scientific, San Francisco, Calif. The capillary end was plugged with glass wool and an appropriate amount of dried adsorbent was dry-packed into the 5-mm i.d. portion of the pipet so as to produce a bed 60 mm in height.

Sample Preparation. A 5.00-g portion of the pentachlorophenol (PCP) sample was weighed into a 4-oz glass bottle and 75 mL of 0.3 N aqueous sodium hydroxide and 15.0 mL of hexane were added. The bottle was capped and placed on a shaker for 15 min. Following layer separation, a 7.5-mL aliquot (equivalent to 2.50 g PCP) of the crude hexane extract was removed and passed through a silicic acid adsorbent column followed by an additional 7.0 mL of hexane with the total eluent being collected in a disposable glass vial. A flow rate of 2 to 3 drops/s was maintained by applying gentle air pressure at the top of the column using a rubber bulb. The silicic acid effluent was then passed through a basic alumina adsorbent column (under the same flow rate conditions) and the hexane effluent discarded. The column was then eluted with 10 mL of 25% carbon tetrachloride in hexane (v/v) and the effluent again discarded. The CDD fraction was then eluted from the column with 5 mL of 50% methylene chloride in hexane (v/v). This fraction was collected in a 3-dram disposable glass vial and evaporated to dryness under a gentle nitrogen stream at room temperature. A 1.0-mL aliquot of chloroform was added to the vial and the residue dissolved with gentle shaking. The chloroform sample concentrate was then analyzed by liquid chromatography.

RESULTS AND DISCUSSION

Optimization of Liquid Chromatography System. The LC method published previously (*5*) for the determination of CDDs in pentachlorophenol was developed using a pellicular reverse-phase column packing and a fixed wavelength (254 nm) ultraviolet detector. Two of the most significant advances

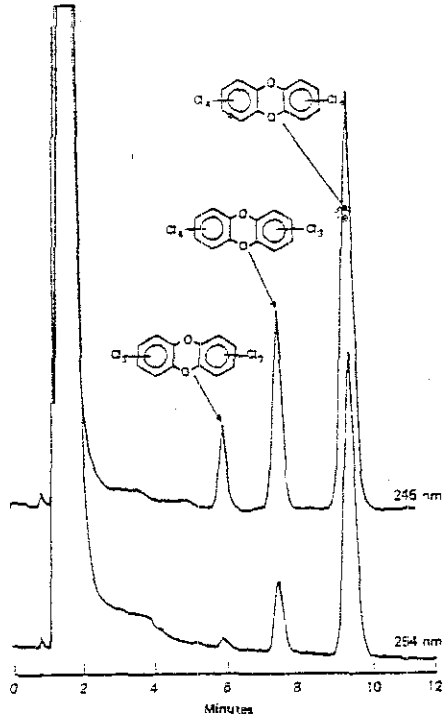

Figure 2. Comparison of detection wavelengths for chlorinated dibenzo-*p*-dioxins. Column, ODS Zorbax; experimental conditions given in text

been the development of stable variable wavelength detectors and bonded phase column packings on porous microparticulate supports. The use of microparticulate column packings and a variable wavelength detector was investigated as a means to achieve a more rapid separation and increased sensitivity.

Examination of the ultraviolet spectrum of hexa-CDD (Figure 1) shows that 254 nm is an inappropriate wavelength for the sensitive detection of this compound. The ultraviolet absorptivity at 245 nm is eight times the absorptivity at 254 nm. Therefore, the LC sensitivity was improved by a factor of eight by monitoring the separation at 245 nm. This increased sensitivity for hexa-dioxin is illustrated in the liquid chromatogram in Figure 2. The sensitivity for hepta-CDD and octa-CDD was also improved.

SAMPLE PREPARATION PROCEDURE

The previous LC method (*5*) was developed specifically for purified pentachlorophenol (DOWICIDE EC-7, Trademark of the Dow Chemical Company) and was not suitable for all types of technical pentachlorophenol because of interferences in the hexa-CDD region of the chromatogram. Impurities present in commercial pentachlorophenol include chlorodibenzofurans (CDBFs), chlorodiphenyl ethers (CDPEs), chlorophenoxy phenols (CPPs), polychlorinated benzenes, and polychlorinated biphenyls in addition to CDDs. The extraction–ion exchange procedure described previously removed the chlorophenols and CPPs from the CDD fraction but no separation of the neutral impurities was obtained.

The extraction-adsorption chromatography procedure described here eliminates all known interferences in pentachlorophenol from the hexa-CDD retention time in the reverse-phase LC separation. The procedure involves dissolving the sample in aqueous caustic which is then extracted with hexane. The hexane extract is passed through a disposable bed of silica gel which retains any chlorophenols, CPPs, or other polar impurities extracted from the aqueous solution.

The hexane solution is then passed through a disposable bed of basic alumina which retains the CDDs, CDBFs, and CDPEs while any chlorobenzenes or chlorobiphenyls present

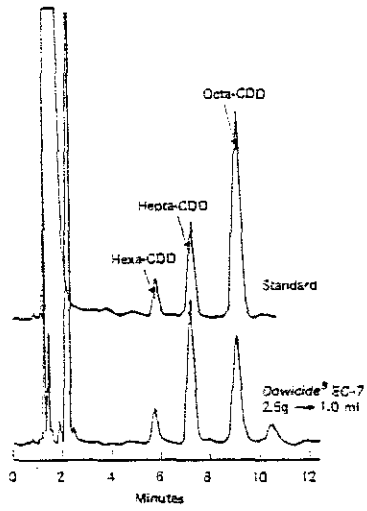

Figure 3. Determination of chlorinated dibenzo-*p*-dioxins in pentachlorophenol. Column, ODS Zorbax; conditions in text. Standard concentrations: hexa-CDD = 2.0 μg/mL, hepta-CDD = 8.5 μg/mL, octa-CDD = 25 μg/mL

Table I. Recovery Data for Chlorodibenzo-*p*-dioxins

	Hexa-CDD	Hepta-CDD	Octa-CDD
High level spike	4.27 ppm	17.08 ppm	51.25 ppm
No. 1	4.35 (102%)	16.65 (97%)	49.11 (96%)
No. 2	4.44 (104%)	16.93 (99%)	50.84 (99%)
No. 3	4.58 (107%)	17.02 (100%)	50.75 (99%)
Specification level spike	0.99 ppm	9.89 ppm	19.78 ppm
No. 1	1.02 (103%)	10.47 (106%)	20.82 (105%)
No. 2	0.95 (96%)	9.79 (99%)	19.89 (101%)
No. 3	0.96 (97%)	9.74 (99%)	19.46 (98%)
No. 4	0.98 (99%)	9.93 (100%)	19.53 (99%)
No. 5	1.04 (105%)	10.03 (101%)	19.26 (97%)
Low level spike	0.095 ppm	0.563 ppm	0.936 ppm
No. 1	0.077 (81%)	0.537 (95%)	0.921 (98%)
No. 2	0.069 (73%)	0.534 (95%)	0.990 (105%)
No. 3	0.098 (103%)	0.518 (92%)	0.912 (97%)
Av recovery	(97.3%)	(98.4%)	(99.4%)

tetrachloride in hexane is then passed through the column to selectively elute the CDPEs. The CDD fraction is eluted by passing 5 mL of 50% methylene chloride in hexane through the column. The effluent is evaporated to dryness using a stream of nitrogen at room temperature and the residue is redissolved in chloroform and analyzed by LC.

An example of the LC separation for a typical sample of purified pentachlorophenol is illustrated in Figure 3. This CDD fraction concentrate was obtained from 2.5 g of pentachlorophenol with the residue dissolved in 1.0 mL of chloroform. The sample contained 0.6 ppm hexa-CDD, 5.2 ppm hepta-CDD, and 5.2 ppm octa-CDD. Detection limits of 50 ppb for hexa-CDD and 100 ppb for hepta- and octa-CDD may be achieved by reducing the volume of chloroform used to dissolve the CDD fraction to 250 μL.

The effectiveness of the sample cleanup procedure is illustrated in the series of chromatograms in Figure 4. Figure 4a represents the LC separation of the total nonphenolic impurity fraction eluted with hexane off the silica gel column. Chromatogram 4b represents the hexane effluent from the basic alumina column containing primarily chlorobenzenes, chlorobiphenyls, and chlorodiphenyl ethers. Separation 4c

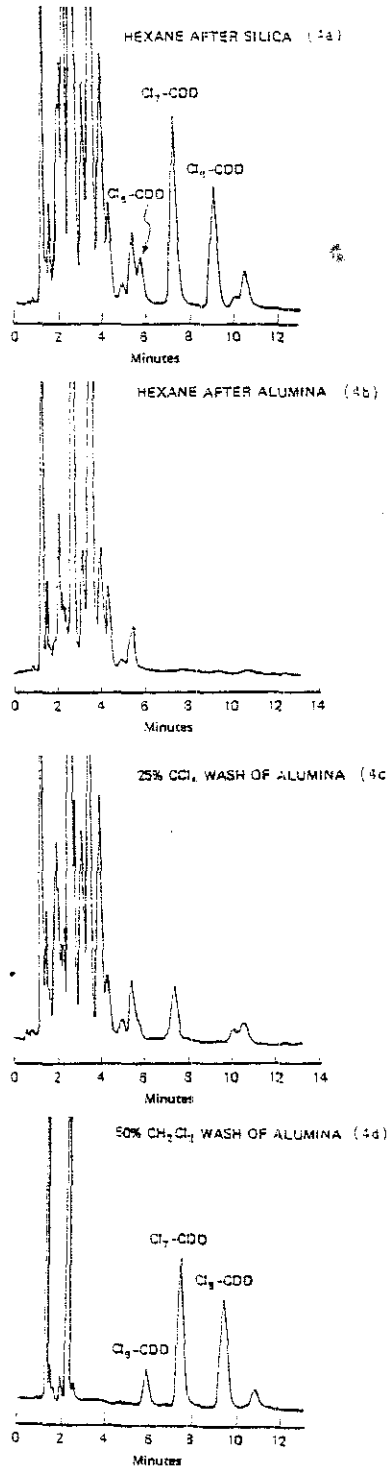

Figure 4. Liquid chromatograms of fractions from cleanup procedure. Column, ODS/Zorbax; conditions as in text

represents primarily CDPEs eluted with the 25% carbon tetrachloride in hexane while the separation in Figure 4d is of the CDD fraction.

The CDD fraction also contains CDBFs but these impurities do not interfere with the determination of the CDDs because of the unusual selectivity of this LC system. The necessary selectivity was obtained using pure methanol as the mobile phase on the ODS/Zorbax column which causes all hexa-CDD isomers to elute in a single symmetrical peak. The two hepta-CDD isomers also elute in a single peak resulting in a simple three-peak chromatogram that permits rapid and accurate quantitation. This is a marked contrast to GC or GC-MS where up to six partially resolved peaks are obtained

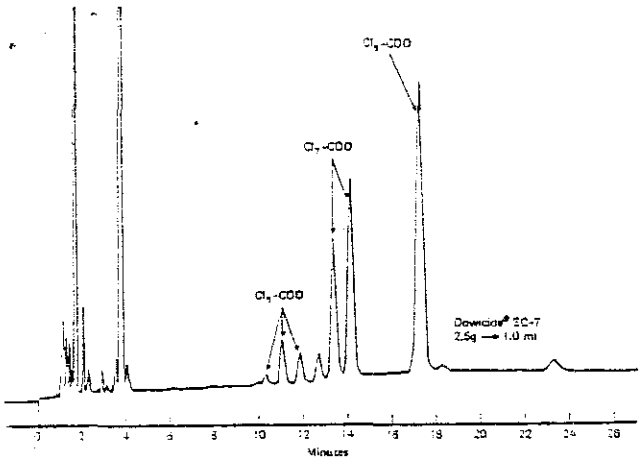

Figure 5. Separation of chlorodibenzo-*p*-dioxin isomers by liquid chromatography. Column, ODS/Zorbax at 55 °C; mobile phase, 15% water in acetonitrile at 2 mL/min; detector 0.01 AUFS at 245 nm; injection, 5 μL of DOWICIDE EC-7 concentrate 2.5-g sample in 1.0 mL chloroform

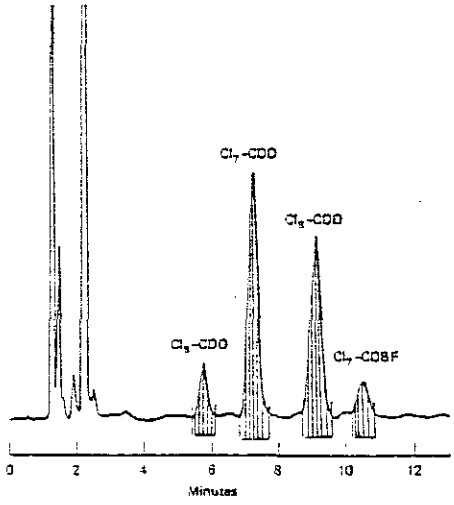

Figure 6. Trapping LC peaks for identification. Column, ODS/Zorbax. Conditions listed in text

Table II. Precision Data for Chlorodibenzo-*p*-dioxins

Run No.	Hexa-CDD, ppm	Hepta-CDD, ppm	Octa-CDD, ppm
1	0.15	1.09	2.28
2	0.14	0.99	2.07
3	0.16	1.03	2.24
4	0.16	1.11	2.19
5	0.16	1.13	2.28
6	0.16	1.08	2.44
7	0.16	1.15	2.34
8	0.16	1.12	2.28
9	0.15	1.11	2.40
10	0.16	1.04	2.27
Av	0.16	1.08	2.28
Rel std dev	(±9.1%)	(±9.1%)	(±8.9%)

for hexa-CDD and where CDDs and CDBFs are not completely separated. The CDBFs do not interfere with the determination of CDDs by LC because of the column selectivity using methanol as the eluent. Additional selectivity is inherent due to reduced UV sensitivity of the CDBFs at 245 nm. DOWICIDE EC-7 typically contains less than 0.5 ppm of a particular hexa-CDBF isomer which elutes in the region of hepta-CDDs. For DOWICIDE EC-7 this is the only known interference for the LC procedure. Because of typical

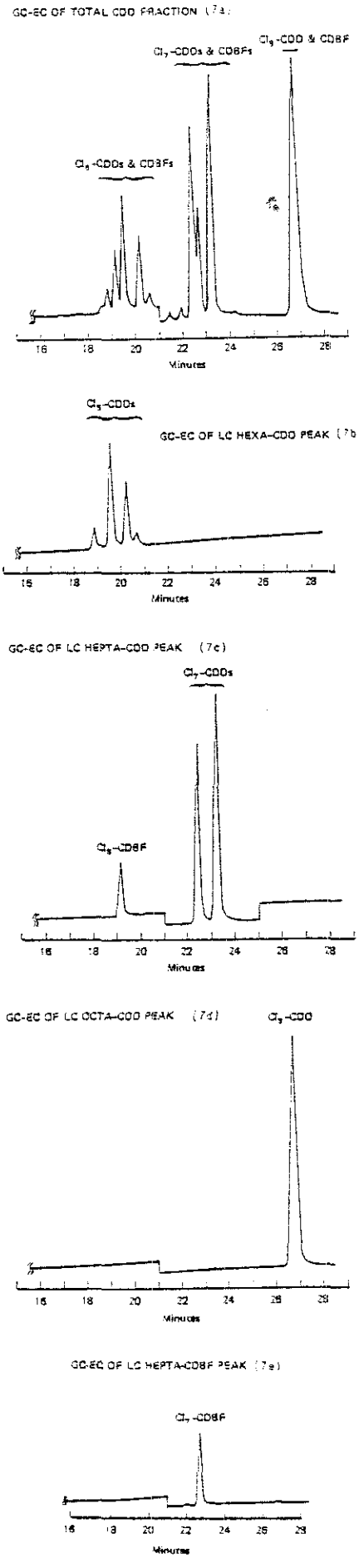

Figure 7. GC-EC examination of LC peaks. Conditions in text

Table III. DOWICIDE EC-7 Correlation Data—LC and GC-MS

DOWICIDE EC-7, Lot No.	Hexa-CDD, ppm		Hepta-CDD, ppm		Octa-CDD, ppm	
	LC	GC-MS	LC	GC-MS	LC	GC-MS
1	N.D.[a]	0.1	0.6	0.4	0.9	0.6
2	N.D.	0.1	0.5	0.6	1.2	1.5
3	0.6	0.8	5.1	5.1	4.1	4.6
4	0.2	0.3	1.5	1.5	2.4	2.2
5	N.D.	N.D.	0.3	0.2	0.7	0.7
6	0.3	0.4	2.0	1.4	1.9	1.4
7	0.4	0.7	3.7	3.8	3.3	3.1
8	N.D.	N.D.	0.4	0.3	1.6	1.4
9	0.7	1.2	10.8	11.1	28.5	33.0
10	0.2	0.3	1.1	1.1	1.3	1.3

[a] *N.D. indicates "not detected" with a limit of detection of 0.1 ppm for hexa-CDD.*

concentration differences between hexa- and hepta-chlorinated species (typical: hepta's > 10 × hexa's) this interference becomes insignificant relative to the limits of error prescribed for this technique. By increasing the LC column temperature to 55 °C and using acetonitrile/water as eluent some CDD isomer separation was achieved but this was considered undesirable for the intended application (Figure 5).

Further proof of the specificity of the LC method for CDDs was obtained by collecting each CDD peak as it eluted from the LC column (Figure 6) during an actual analysis run. These fractions were evaporated under nitrogen, diluted to an appropriate volume, and re-examined by GC/EC. Chromatograms for these separations appear in Figure 7 (a–e). Figure 7a is the same total CDD fraction examined by temperature-programmed GC-EC showing the hexa-, hepta-, and octa-CDDs and CDBFs elution zones. Figure 7(b–e) are GC/EC chromatograms of each LC peak trapped as they eluted from the Zorbax/ODS column. Component identifications appearing on these GC/EC chromatograms were obtained by GC/MS using the same chromatographic conditions and column packings as described. The GC/EC chromatogram of the LC hexa-CDD peak (Figure 7b) shows at least six different components; each was identified as a hexa-CDD isomer. Similarly, the LC hepta-CDD peak (Figure 7c) contains both possible isomers of hepta-CDD and a minor component identified as a hexa-CDBF. The other minor hexa-CDBF shown in Figure 7a does not interfere with hepta-CDDs for this LC separation. Figure 7d illustrates the GC/EC chromatogram of the LC octa-CDD peak. Although the GC column packing described will not separate octa-CDD from octa-CDBF, GC/MS verified that the component observed was octa-CDD. In addition, an octa-CDBF standard chromatographed on this LC system demonstrated an elution time of 16 min as compared to 9 min for octa-CDD. Examination of the latest eluting LC peak by GC/EC as shown in Figure 7e indicated it to be the major hepta-CDBF isomer present in DOWICIDE EC-7. The other three possible hepta-CDBF isomers are typically present at concentrations too low to be observed by LC under these conditions.

METHOD VALIDATION

The method was validated by obtaining recovery and precision data and analyzing ten random production lots by both LC and GC-MS and comparing the results. Recoveries for the method were obtained by spiking samples of an exceptionally pure lot of DOWICIDE EC-7 with known amounts of CDDs and carrying them through the procedure. The results were quantitated with external standards not carried through the method. The DOWICIDE EC-7 used in the recovery studies were analyzed for CDDs prior to spiking and recoveries were corrected for the low levels of CDDs present in the sample. Samples were spiked with CDDs near the specification limit for purified pentachlorophenol (less than 1 ppm hexa-CDD and less than 30 ppm octa-CDD), at twice the specification level and at one-tenth the specification CDD level. The results of the recovery studies are summarized in Table I.

The poor recovery of hexa-CDD at low levels is due to an LC detection problem rather than loss of the CDD. The sample used in the recovery work contained 0.09 ppm hexa-CDD which was about equal to the 0.095-ppm spike. The combination of large background correction and operation near the LC detection limit prevented accurate determination of the recovery.

The precision of the method was determined by analyzing ten samples of a single specimen of DOWICIDE EC-7. The results are summarized in Table II. Further evidence of method validity was obtained by analyzing ten samples by both LC and the GC-MS method of Blaser (3). The results of this study are summarized in Table III.

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